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L15	L14 same l4	66	L15
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L9	l6 with l2	81	L9
L8	L7 same l1	2	L8
L7	L6 same l2	101	L7
L6	zwitterionic	17523	L6
L5	L4 and l3	81	L5
L4	dna or nucleic or gene or plasmid or polynucleotide	405758	L4
L3	l2 with l1	142	L3
L2	pka	18490	L2
L1	lipid or amphiphile or liposome	134919	L1

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L5: Entry 14 of 16 File: DWPI Jul 22, 2004

DERWENT-ACC-NO: 2002-188239
DERWENT-WEEK: 200449

TITLE: Microparticle useful for the delivery of bioactive agent, e.g. nucleic acid comprises polymeric matrix, an anionic and zwitterionic lipid and nucleic acid molecule

Basic Abstract Text (1):
NOVELTY - A microparticle having diameter of less than 100 microns, comprising a polymeric matrix (a), a lipid (l1) having a pKa of less then 2.5 or a zwitterionic lipid (l2) and a nucleic acid molecule (c), is new. The microparticle is not encapsulated in a liposome and does not comprise a cell.

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L11 and polymer	267

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DATE: Friday, January 21, 2005 Printable Copy Create Case

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ			
L12	l11 and polymer	267	L12
L11	l10 and l4	295	L11
L10	L9 and lipid	301	L10
L9	wolff and l1	434	L9
L8	amphiphile with l1	7	L8
L7	amphiphile same l3	7	L7
L6	l3 same polymer	8	L6
L5	L4 with l3	16	L5
L4	dna or nucleic or gene or vector	619628	L4
L3	l2 with l1	119	L3
L2	lipid or amphiphile	111911	L2
L1	pka	18490	L1

END OF SEARCH HISTORY

L5: Entry 37 of 81 File: PGPB Apr 10, 2003

PGPUB-DOCUMENT-NUMBER: 20030069392
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030069392 A1

TITLE: Cationic lipids

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lin, Kuei-Ying	Fremont	CA	US	
Mattuecci, Mark D.	Burlingame	CA	US	

US-CL-CURRENT: 530/330; 530/331

CLAIMS:

1. A compound having the structure A 19wherein each R is independently hydrogen or a lipophilic moiety, provided that both R are not hydrogen; R.sup.1 and R.sup.2 are independently hydrogen, --(CH.sub.2).sub.z--N(R.s- up.4).sub.2, --(CH.sub.2).sub.zNR.sup.4--C(NH)--N(R.sup.5).sub.2, or W.sup.1, provided that at least one of R.sup.1 and R.sup.2 is W.sup.1; each R.sup.3 is independently hydrogen, alkyl (C.sub.1-10), --CH.sub.2--(CF.sub.2).sub.p--CF.sub.3, aryl, a protecting group, or both R.sup.3 together are a protecting group, or one R.sup.3 is hydrogen and the other R.sup.3 is --C(O)CH.sub.2NH.sub.2 or --C(O)CHCH.sub.3NH.sub.2, provided that both R.sup.3 are not aryl; each R.sup.4 is independently hydrogen, alkyl (C.sub.1-6), a protecting group, --CH.sub.2--(CF.sub.2).s- ub.p--CF.sub.3, or both R.sup.4 together are a protecting group; each R.sup.5 is independently hydrogen, alkyl (C.sub.1-6), a protecting group, or both R.sup.5 together are a protecting group; each W.sup.1 is independently a cationic group, at least one of which has a pka of about 6.0-7.5; m is an integer having the value 0, 1, 2, 3 or 4; n is an integer having the value 0, 1, 2, 3 or 4; p is an integer having the value 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; s is an integer having the value 0, 1 or 2; z is an integer having the value 1, 2, 3, or 4; positions designated * are carbon atoms with linked substutuents in the R, S or RS configuration; and the salts, tautomers, solvates, resolved, partially resolved and unresolved enantiomers, purified, partially purified and unpurified positional isomers or diastereomers thereof.

2. The compound of claim 1 wherein W.sup.1 is 20

3. The compound of claim 2 wherein each W.sup.1 independently is B, C, or D 21

4. The compound of claim 1 wherein each R is independently a group containing about 10-50 linked carbon atoms.

5. The compound of claim 4 wherein m and n are both 0 and s is 1.

6. The compound of claim 5 wherein each group containing about 10-50 linked carbon atoms is independently alkyl (C.sub.10-22), a mono-, di- or tri-unsaturated alkenyl (C.sub.10-22) group, or one is a cholesteryl moiety and the other is hydrogen.

7. The compound of claim 6 wherein each group containing about 10-50 inked carbon atoms is independently alkyl (C.sub.10-16).

8. The compound of claim 7 wherein each W.sup.1 independently is 22

9. The compound of claim 8 wherein each W.sup.1 independently is B, C, or D 23

10. A compound having the structure A1 24wherein each R is independently hydrogen or a lipophilic moiety, provided that both R are not hydrogen; R.sup.1 and R.sup.2 are independently hydrogen, --(CH.sub.2).sub.z--N(R.s- up.4).sub.2 --(CH.sub.2).sub.zNR.sup.4--C(NH)--N(R.sup.5).sub.2, or W.sup.1, provided that at least one of R.sup.1 and R.sup.2 is W.sup.1; each R.sup.3 is independently hydrogen, alkyl (C.sub.1-10), --CH.sub.2--(CF.sub.2).sub.p--CF.sub.3, aryl, a protecting group, or both R.sup.3 together are a protecting group, or one R.sup.3 is hydrogen and the other R.sup.3 is --C(O)CH.sub.2NH.sub.2 or --C(O) CHCH.sub.3NH.sub.2, provided that both R.sup.3 are not aryl; each R.sup.4 is independently hydrogen, alkyl (C.sub.1-6), a protecting group, --CH.sub.2--(CF.sub.2).s- ub.p--CF.sub.3, or both R.sup.4 together are a protecting group; each R.sub.5 is independently hydrogen, alkyl (C.sub.1-6), a protecting group, or both R.sup.5 together are a protecting group; each W.sup.1 is independently 25m is an integer having the value 0, 1, 2, 3 or 4; n is an integer having the value 0, 1, 2, 3 or 4; p is an integer having the value 0, 1, 2, 3, 4, 5, 6, 7, 8 ,9, or 10; s is an integer having the value 0, 1 or 2; z is an integer having the value 1, 2, 3, or 4; positions designated * are carbon atoms with linked substutuents in the R, S or RS configuration; and the salts, tautomers, solvates, resolved, partially resolved and unresolved enantiomers, purified, partially purified and unpurified positional isomers or diastereomers thereof.

11. The compound of claim 10 wherein each W.sup.1 independently is B, C or D 26

12. The compound of claim 10 wherein m and n are both 0 and s is 1.

13. The, compound of claim 10 having the structure 27wherein R is n-C.sub.14H.sub.29.

14. The compound of claim 10 wherein each R is independently a group containing about 10-50 linked carbon atoms.

15. The compound of claim 14 wherein m and n are both 0 and s is 1.

16. The compound of claim 15 wherein each group containing about 10-50 linked carbon atoms is independently alkyl (C.sub.10-22), a mono-, di- or tri-unsaturated alkenyl (C.sub.10-22) group, or one R is a cholesteryl moiety and the other R is hydrogen.

17. The compound of claim 16 wherein each group containing about 10-50 linked carbon atoms is independently alkyl (C.sub.10-16).

18. The compound of claim 17 wherein each W.sup.1 independently is B, C, or D 28

19. A compound having the structure E 29wherein q and r are each independently 0, 1, 2 or 3; each R is independently hydrogen or a lipophilic moiety, provided that both R are not hydrogen; R.sup.11 is a moiety with a pKa of about 6.0-10; and

R.sup.12 is a W.sup.1 moiety with a pKa of about 6.0-7.5.

20. The compound of claim 19 wherein W.sup.1 is 30wherein each R.sup.5 is independently hydrogen, alkyl (C.sub.1-6), a protecting group, or both R.sup.5 together are a protecting group; and z is 1, 2, 3, or 4.

21. A compound having the structure E1 31wherein q and r are each independently 0, 1, 2 or 3; each R is independently hydrogen or a lipophilic moiety, provided that both R are not hydrogen; R.sup.11is --N(R.sup.4).sub.2 or --N(R.sup.14)(R.sup.4) when q is 0 and R.sup.11 is --NH--CH.sub.2--CN, --NH--CH.sub.2-NO.sub.2, --NH--CH.sub.2SO.sub.2R.sup.- 15, --NH--CH.sub.2--C(O)(CH.sub.2).sub.mCH.sub.3, --NH--CH.sub.2(CF.sub.2)- .sub.m(CF.sub.3, or --NH--CH.sub.2O(CH.sub.2).sub.mCH.sub.3, when q is 1, 2, or 3; R.sup.12 is W.sup.1; R.sup.14 is hydrogen or alkyl (C.sub.1-6); R.sup.15 is hydrogen or alkyl (C.sub.1-6); W.sup.1 is 32each R.sup.5 is independently hydrogen, alkyl (C.sub.1-6), a protecting group, or both R.sup.5 together are a protecting group; and z is 1, 2, 3, or 4.

22. The compound of claim 21 wherein W.sup.1 is B, C or D 33

23. The cationic lipid of claim 22 wherein each lipophilic moiety is independently-hydrogen alkyl (C.sub.10-22), a mono-, di-, or tri-unsaturated alkenyl (C.sub.10-22) group, or one R is a cholesteryl moiety and the other R is hydrogen.

24. The cationic lipid of claim 23 wherein R.sup.11 is --NH.sub.2.

25. The cationic lipid of claim 23 wherein q is 0 and r is 1 or q is 1 and r is 0.

26. The cationic lipid of claim 23 wherein both R are the same and are alkyl (C.sub.12-16).

27. A composition comprising the lipid of claim 10 and a colipid.

28. The composition of claim 27 wherein the colipid is DOPE.

29. A composition comprising the lipid of claim 10 and an anionic or polyanionic compound.

30. The composition of claim 29 wherein the anionic or polyanionic compound is a nucleotide analog, a nucleic acid, an oligonucleotide, a peptide or a protein.

31. The composition of claim 30 wherein the nucleic acid is a circular or linear plasmid or is an RNA.

32. The composition of claim 30 wherein the nucleotide analog is HPMPC, PMEA, PMEG or PMPDAP.

33. A cationic lipid of structure A1 or E1 having a moiety with a pKa of about 6.0 to 7.5 wherein the pKa is determined by the process of: (a) preparing a water solution containing a suspension of the HCI salt of the cationic lipid at a concentration of about 2-fold above the cationic lipid's CMC to obtain a cationic lipid suspension; (b) measuring the pH of the cationic lipid suspension; (c) adding 0.1 equivalent of a NaOH solution in water and mixing the NaOH solution into the cationic lipid suspension; (d) measuring the pH of the suspension of step (c) to obtain a pH value; (e) repeating steps (c) and (d) until one has added 1.0 equivalents of the NaOH solution and obtained the pH value at completion of each repetition of step (d); (f) plotting each pH value obtained from each repetition of

step (d) versus the number of equivalents of added NaOH; and (g) determining the pKa of the cationic lipid using an inflection point of the pH versus equivalents of added NaOH curve.

34. A method comprising; (a) preparing a complex of the lipid of claim 10 and a therapeutic agent, a nucleic acid or an oligonucleotide; and (b) introducing the complex into a subject, whereby the therapeutic agent, nucleic acid or oligonucleotide is introduced into the cells of the subject.

35. The method of claim 34 wherein the subject is a mammal.

36. The method of claim 35 wherein the mammal is a rodent, a non-human primate or a human.

37. The method of claim 35 wherein the nucleic acid is an expression vector.

38. The method of claim 35 wherein the therapeutic agent, nucleic acid or oligonucleotide is introduced into the subject's lung or spleen cell.

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L5: Entry 71 of 81 File: USPT Sep 3, 1996

DOCUMENT-IDENTIFIER: US 5552155 A
TITLE: Fusogenic lipsomes and methods for making and using same

Brief Summary Text (16):
The aqueous solution external to the liposome is an aqueous buffer having a pH which is greater than the pK.sub.a of the ionizable lipid in the outermost lipid bilayer. Preferably, when the ionizable lipid is AL-1, the pH of the external aqueous buffer is about 7,5. The liposome can further comprise a neutral, non-bilayer-preferring lipid, for example, dioleoyl phosphatidylethanolamine (DOPE). The liposome can comprise a biologically active agent, which is typically a nucleic acid, an antimicrobial agent, an anticancer agent or an anti-inflammatory agent. The aqueous solution external to the liposome can be a pharmaceutically acceptable aqueous solution, and the liposome composition can be a pharmaceutical composition.

Brief Summary Text (19):
The liposome used in the method of this invention can comprise a biologically active agent, which is typically a nucleic acid, antimicrobial agent, anticancer agent or anti-inflammatory agent. The second lipid bilayer to which the liposome is fused in a controlled manner is preferably the plasma membrane of a cell, most preferably, the plasma membrane of a mammalian cell.

Brief Summary Text (20):
This invention provides a method of introducing a biologically active agent into a cell which comprises preparing a liposome comprising the agent in an aqueous solution so that the aqueous solution is internal and external to the liposome. The liposome comprises an outermost lipid bilayer which comprises a neutral, bilayer-preferring lipid and an ionizable lipid having a cationic headgroup and unsaturated acyl chains. The pH of the internal aqueous solution is less than the pKa of the ionizable lipid in the outermost lipid bilayer. The pH of the external aqueous medium is increased above the pKa of the ionizable lipid in the outermost lipid bilayer so that there is a pH gradient across the outermost lipid bilayer and the ionizable lipid is then accumulated in the inner monolayer of the outermost lipid bilayer. The pH of the internal aqueous solution is increased above the pK.sub.a of the ionizable lipid in the outermost lipid bilayer prior to contacting the cell with the liposome. Preferably, the cell is a mammalian cell

Detailed Description Text (2):
This invention provides a liposome composition which comprises a liposome having: (i) an outermost lipid bilayer comprising a neutral, bilayer-preferring lipid and a fusion-promoting effective amount of an ionizable lipid comprising a protonatable, cationic headgroup and an unsaturated acyl chain; (ii) a compartment adjacent to the outermost lipid bilayer which comprises an aqueous solution (the "internal aqueous solution") having a first pH. The composition also comprises an aqueous solution external to the liposome having a second pH. The first pH is less than the pKa of the ionizable lipid in the outermost lipid bilayer and the second pH is greater than the pKa of the ionizable lipid in the outermost lipid bilayer, whereby there is a pH gradient across the outermost lipid bilayer, and the ionizable lipid is accumulated in the inner monolayer of the outermost lipid bilayer in response to the pH gradient.

Detailed Description Text (11):
The liposome has a compartment adjacent to its outermost lipid bilayer which comprises an aqueous solution (the "internal aqueous solution") having a first pH. The liposome is suspended in an aqueous solution (the "external aqueous solution") having a second pH. Typically, the liposome is prepared in an aqueous solution, which is both entrapped by the liposome, and in which the liposome is suspended. Accordingly, the internal and external aqueous solutions generally initially have the same composition, and also, the same pH. Their pH is less than the pKa of the ionizable lipid in the liposome's outermost lipid bilayer.

Detailed Description Text (12):
A compound's pK.sub.a, that is, its acid dissociation constant, is the pH at which the compound is half-dissociated, that is, the pH at which about half of the molecules of the compound present in solution are deprotonated. pK.sub.a can be defined by the formula: log ([HA]/[H.sup.+] [A.sup.-]), where HA is the protonated compound and A.sup.- is the deprotonated compound. The Henderson-Hasselbach equatin (pH=pK.sub.a + log ([A-]/HA])) describes the relationship between the pH of a solution and the relative concentrations of the protonated and deprotonated forms of a compound present in solution. At a pH greater than its pK.sub.a in a lipid bilayer, more than half of the ionizable lipid present in the bilayer will be deprotonated, and hence, neutral. Determination of an ionizable lipid's pKa can be accomplished by well known and readily practiced means, for example, by TNS fluorescence titrations.

Detailed Description Text (16):
The second pH, that is, the pH of the external aqueous solution, is greater than 6.7 when the liposome comprises AL-1/EPC/Chol or AL-1/EPC/Chol/DOPE; preferably, the second pH is about 7.5. However, incorporation of other lipids into AL-1/EPC/Chol or AL-1/EPC/Chol/DOPE liposomal bilayers can affect the pKa of AL-1 therein. Ionizable lipids other than AL-1 can have different pKa's than AL-1. Accordingly, the first and second pH's may vary from the preferred pH values when the composition of the liposome is altered.

Detailed Description Text (17):
When the first pH is less than the ionizable lipid's pKa in the outermost lipid bilayer, the second pH is greater than the pKa, and the ionizable lipid is accumulated in the inner monolayer of the outermost lipid bilayer, the positive charge of the ionizable lipid is substantially absent from the outer monolayer, and is shielded from exposure to the external environment. When administered to animals, positively charged lipid can cause toxic side effects and can promote opsonization, the binding of plasma proteins to the liposome's outer surface, thereby promoting clearance of liposomes from the animal's circulation. Accumulating the positive charge in the inner monolayer minimizes the potential for toxic side effects and for opsonization.

Detailed Description Text (24):
The liposome can comprise a biologically active agent, a term that includes traditional pharmaceuticals, and related biologically active compounds or compositions of matter, having biological activity in an animal or on an animal's cells in vitro. Bioactive agents include, but are not limited to: antibacterial agents, antiviral agents, antifungal agents, anti-parasitic agents, tumoricidal agents, anti-metabolites, carbohydrates, polypeptides, peptides, proteins, toxins, enzymes, hormones, neurotransmitters, glycoproteins, lipoproteins, immunoglobulins, immunomodulators, vasodilators, dyes, radiolabels, radio-opaque compounds, fluorescent compounds, polysaccharides, cell receptor binding molecules, antiinflammatory agents, mydriatic compounds, local anesthetics, narcotics, anti-glaucomic agents, vitamins, nucleic acids, polynucleotides, nucleosides, nucleotides, MRI and radio contrast agents.

Detailed Description Text (29):
When fusion of the liposome to a second lipid bilayer is desired, the liposome's internal pH is raised above the ionizable lipid's pK.sub.a in the bilayer such that the pH gradient is degraded. The protonated/charged ionizable lipid accumulated in the inner monolayer of the outermost lipid bilayer is substantially deprotonated when the pH of the internal aqueous solution adjacent to the bilayer rises above the lipid's pKa in the bilayer. The substantially deprotonated/neutral ionizable lipid is then about evenly distributed in the outermost lipid bilayer, that is, about 50 percent is in the inner monolayer and about 50 percent is in the outer monolayer. The neutral lipid in the outer monolayer can promote fusion to other lipid bilayers. The pH gradient can be degraded by administering the liposome composition to an animal and allowing the gradient to gradually dissipate in the animal as protons stored in the liposome leak into the external environment. As the liposome's internal pH approaches physiological pH, ionizable lipids with pK.sub.a 's less than physiological pH are substantially deprotonated. pH gradient degradation can also be accomplished the use of ionophores, for example, nigericin, which facilitate the transport of ions across lipid bilayers, or by the addition of ions, for example, ammonium ions, which can cross lipid bilayers in their neutral form. When the internal pH is raised above its pK.sub.a, the charged ionizable lipid is substantially deprotonated; the neutral lipid is distributed about evenly between the inner and outer monolayers of the outermost lipid bilayer.

Other Reference Publication (8):
Fraley, et al., "Introduction of Liposome-encapsulated SV 40 DNA into Cells", J. Biol. Chem, 255(21), 10431-10435, 1980.

CLAIMS:

1. A liposome composition comprising:

(a) a unilamellar liposome having:

(i) a bilayer which comprises a bilayer forming phosphatidylcholine and between about 1 mole percent and about 20 mole percent of a fusogenic lipid selected from the group consisting of 1-N,N-dimethylamino dioleoyl propane, 1-oleoyl-2-hydroxy-3-N,N-dimethylamino propane, 1,2-diacyl-3-N,N-dimethylamino propane and 1,2-didecanoyl-1-N,N,-dimethylamino propane; and

(ii) an internal compartment comprising an aqueous solution; and

(b) an aqueous solution external to the liposome,

wherein the pH of the internal aqueous solution is less than the pKa of the fusogenic lipid in the bilayer and the pH of the external aqueous solution is greater than the pKa of the fusogenic lipid in the bilayer,

whereby there is a pH gradient across the bilayer, and

whereby the fusogenic lipid is accumulated in the bilayer's inner monolayer.

11. The liposome composition of claim 10, wherein the biologically active agent is a nucleic acid, an antimicrobial agent, an anticancer agent or an anti-inflammatory agent.

14. A method of controlling the fusion of a liposome to a cell membrane which comprises:

(a) preparing the liposome with a bilayer-forming phosphatidylcholine, a fusogenic lipid selected from the group consisting of 1-N,N-dimethylamino dioleoyl propane, 1-oleoyl-2-hydroxy-3-N,N-dimethylamino propane, 1,2-diacyl-3-N,N-dimethylamino

propane and 1,2-didecanoyl-1-N,N,-dimethylamino propane, and an aqueous solution having a pH that is less than the fusogenic lipid's pKa in the bilayer, so that the fusogenic lipid comprises from about 5 mole percent to about 20 mole percent of the bilayer and the aqueous solution is both internal and external to the resulting liposome;

(b) increasing the pH of the aqueous solution external to the liposome above the pKa of the fusogenic lipid in the bilayer, whereby there is a pH gradient across the bilayer and whereby the fusogenic lipid is accumulated in the bilayer's inner monolayer; and

(c) causing the pH gradient to decay such that the pH of the internal aqueous solution is greater than the pKa of the fusogenic lipid in the bilayer.

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L15: Entry 58 of 66 File: USPT Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6217900 B1
** See image for Reexamination Certificate **
TITLE: Vesicular complexes and methods of making and using the same

Brief Summary Text (26):
The cationic charged end of the local anesthetic binds to anionic groups on nucleic acid molecules at a pH below the pKa of the amine, for example at physiological pH. The local anesthetics-nucleic acid complex becomes more charge neutral, hydrophobic and lipophilic under these conditions and can partition into/through the lipid membrane of cells, delivering the nucleic acid to the cell. Local anesthetics have been shown to have higher lipid partition coefficients as a neutral species.

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L15: Entry 66 of 66 File: DWPI Dec 10, 1996

DERWENT-ACC-NO: 1997-042308
DERWENT-WEEK: 199704

TITLE: Enhancing membrane permeability of negatively charged polymers - using an enhancer molecule such as amino-caprylic acid

Basic Abstract Text (2):
In processes (A) and (B) the PEM is provided in an amt. of at least one PEM per negative charge on the NCP. The NCP is RNA or DNA and the PEM ion-pairs with the phosphate gps. in the NCP. Formation of the ion pair increases the intrinsic hydrophobicity of the polynucleotide, allowing the polynucleotide to diffuse across a cell membrane. The PEM may be provided co-encapsulated within a liposome with the NCP. The cationic gp. in (A) is an aminobenzyl gp. or an imidazole gp. with a pKa of 4.0-5.0. The anionic gp. is a carboxylate gp. having a pKa of 4.5-5.5. The PEM also comprises a linker between the cationic and anionic gps. The linker is a hydrocarbon chain or a simple or complex aromatic hydrocarbon. In (B) the PEM may comprise a guanidinium gp. or an amine gp. In (C) and (D) the ligand is selected from monoclonal antibodies (or fragments of these), peptides, proteins, carbohydrates and vitamins. The biological labile bond is e.g. an ester, carbamoyl or peptide bond.

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